

### **Remarks**

Upon entry of the foregoing amendments, claims 1-101 are pending in this application. Claims 12-51 and 63-101 have been withdrawn from consideration as being directed to a non-elected invention. Applicant maintains the right to file one or more continuation or divisional applications on any canceled subject matter.

### ***Double Patenting Rejection***

Claims 1, 8, 9, 52, 56, 59, 60 and 62 are rejected under non-statutory obviousness-type double patenting as allegedly being unpatentable over Claims 1, 10, 13, 14, 15, 24 and 25 of US Patent No. 7,384,640 in view of Agren et al., (J. Immunol. 1999. 162 (2): 2432-2440).

Applicant respectfully requests that these rejections be held in abeyance until patentable subject matter is determined.

### ***Rejections under 35 U.S.C §112***

Claims 10, 52 and 61 stand rejected under 35 USC §112, Second Paragraph as allegedly being indefinite for failing to point out and distinctly claiming the subject matter of the invention.

a) The Examiner alleges that the preamble of the above mentioned claims are drawn to a method of immunizing a mammalian host, but that the recited steps within the method do not state what the host is immunized from. Applicant traverses this rejection.

Applicant submits that Claim 10 of the present application is a composition claim directed to an immunogenic composition and is not a method claim. Applicant respectfully submits that the rejection is improper and should be withdrawn.

Applicant wishes to further submit that Claims 52 and 61 are directed to a method of immunizing a mammalian host comprising administering to the host an immunogenic composition comprising a cholera holotoxin (CT) and an antigen covalently associated with the CT. Applicant's invention relates to the cholera holotoxin conjugated to any antigen and it's ability to increase the immunogenic properties of that or any conjugated antigen, as exemplified in the present specification. As demonstrated in the Examples section, a wide range of antigens (A $\beta$  1-7 peptide, Meningococcal LOS, Group B strep antigen (GBSIII) and Chlamydial LOS) were shown to have increased immunogenic properties when conjugated with CT. Applicant submits that there should be no limitation on what the mammalian host is immunized against. Claims 52 and 61 should not be limited to any particular disorder or disease. Applicant respectfully requests that the rejection is improper and should be withdrawn.

b) The Examiner is of the opinion that the scope of claims 10 and 61 is uncertain since a trademark cannot be used properly to identify any particular material or product. The Examiner contends that the trademarks STIMULON™, QS-21™, and MPL™ are indefinite. Applicant submits that the trademark STIMULON™ is not used in either of claims 10 or 61. Applicant also wishes to submit that claims 10 and 61 have been amended by deleting the term MPL™ and to use the chemical name "3-O-deacylated monophosphoryl lipid A" which was stated in the claims as originally filed. Applicant has also amended claims 10 and 61 by removing the trademark QS-21 and replacing it with the term "a saponin". QS-21 is well known to those skilled in the art to be a purified saponin.

Applicant believes that the amendments to the claims and arguments presented render the rejection under 35 USC §112, second paragraph moot and withdrawal of these rejections is respectfully requested.

#### *Claim Rejections- 35 USC §103*

Claims 1-11 and 52-62 are rejected under 35 USC §103 (a) as allegedly being unpatentable over Jobling et al., (WO 00/18434) in view of Agren et al., (J. Immunol. 1999, 162(2): 2432-2440, hereafter "Agren"). Applicant traverses this rejection.

The present invention relates to a mutant cholera holotoxin which functions as both an adjuvant and an antigen carrier. An embodiment of the present invention is directed at a mutated cholera toxin (CT) that is genetically modified at residue 29 of the A subunit wherein the amino acid substitution is not an aspartic acid. In some embodiments the amino acid substitution at position 29 is a histidine (CT<sub>E29H</sub>). In certain embodiments of the present invention the antigen is covalently associated with the CT<sub>E29H</sub>. Throughout the Examples section of the present specification a number of different classes of antigens, including carbohydrate antigens, peptide antigens and lipooligosaccharide antigens were conjugated to mutant CT<sub>E29H</sub> using various chemistries. In particular, conjugates were made with CT<sub>E29H</sub> and (1) the group B strep antigen (GBS III), or (2) the amino-terminal amino acids 1-7 of the 42 amino acid β-amylod peptide, or (3) the meningococcal lipooligosaccharide (LOS) containing the inner core saccharide structures of the molecule. The results shown in the present specification show that mutant CT<sub>E29H</sub> functions both as a carrier protein and as an adjuvant while maintaining intrinsic adjuvant properties. The various CT<sub>E29H</sub> conjugates show superior antigen specific immune response when subjects were administered with the conjugates versus administration of the individual components separately.

In contrast, Agren teaches a gene fusion product of the A subunit of CT conjugated to a B-cell targeting moiety, DD (Ig binding fragment D of Staphylococcus aureus protein A). The DD

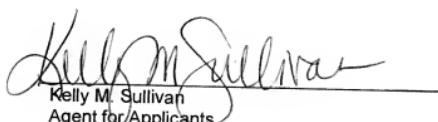
portion of the CT-DD conjugate targets the conjugate to B cell and further adds to the adjuvanting properties of CT. Agren teaches an enhanced immune response to the conjugated adjuvants when co-administered with different antigens. Agren teaches combination of two adjuvants and the combination's enhanced ability to immunomodulate, while Applicant's claimed invention is a mutated CT covalently associated with a number of different, separate antigens, not another adjuvant. Applicant demonstrates an enhanced antigen specific immune response when the CT is covalently associated with an antigen as compared to separate administration of CT and antigen.

The Examiner has failed to prove a *prima facie* case of obviousness based on Jobling in view of Agren. The Examiner states on page 7 of the Office Action dated July 9, 2008 that it would have been *prima facie* obvious at the time of the applicant's invention to apply Agren's covalently associated cholera holotoxin with an antigen that target powerful bacterial enzymes. Agren does not, in fact, teach a covalently associated CT with an antigen, but a genetically constructed CT with another adjuvant, not an antigen.

In light of the arguments presented herein Applicant respectfully submits that the rejection under 103(a) is improper and should be withdrawn.

### ***Conclusion***

In conclusion, this reply is believed to be a full response to the outstanding Office Action. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned representative at the Examiner's earliest convenience.



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